REMARKS

Claims 27-34 are pending.

Applicants note that the Office action summary and PAIR indicate that the Office action mailed 11/16/07 is a non-final Office action but that page 9 of the Office action indicates it is final. Applicants discussed the finality of the Office action with Examiner O'Hara on February 19, 2008. Applicants thank Examiner O'Hara for clarifying that the Office action mailed 11/16/07 is non-final.

Applicants respectfully traverse the present rejections.

35 U.S.C. § 101

Claims 27-34 remain rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. According to the Office action, the remaining issue "is not whether the expression levels based upon DNA were significantly different in the tested tumors, but rather whether this data makes it more likely than not that the protein encoded by the gene is overexpressed."

US Patent No. 7,208,308 as evidence of utility:

Applicants respectfully maintain that issued US Patent No. 7,208,308 (the "'308 patent") is persuasive evidence that the gene amplification of PRO347 provides a specific and substantial utility for the claimed polypeptide. The Office action alleges that "upon examination of [US Patent No. 7,208,308], it is not clear that the utility requirement was considered specific and substantial because of amplification of genomic DNA, or because it was determined that the polypeptide was a serine protease, and therefore the protein had a specific and substantial utility." Page 3 of the Office action. Applicants respectfully disagree. The prosecution history of the '308 patent demonstrates that Applicants of the '308 patent asserted and relied on utility based on gene amplification.

In particular, Example 92 of the '308 patent is substantially identical to Example 28 of the present application with the main difference being that different PRO nucleic acids were

analyzed in Example 92 of the '308 patent than in Example 28 of the present application. Before being allowed, the claims in the '308 patent were rejected for alleged lack of utility. In response to that rejection, the Applicant of the '308 patent stated "Applicants have asserted utility for the instantly claimed PRO343 polypeptide based on amplification of the PRO343 gene in the 'gene amplification assay' described in the instant specification in Example 92." *See* page 4 at Tab A, Amendment and Response filed 11/9/05. Indeed, the Notice of Allowability for the '308 patent issued in response to the amendment filed August 15, 2006. *See* Tab B, Notice of Allowability. That August 15, 2006 Amendment was the Applicants submission of the declaration of Randy Scott, Ph.D. *See* Tab C, Amendment and Response dated 8/15/06. Applicants submitted the same declaration of Randy Scott in the present application on December 7, 2006. In his declaration, Dr. Scott testifies about the utility of DNA microarrays. Example 92 of the '308 patent and Example 28 of the present application use microarray technology to identify amplified genes. Dr. Scott also testified that in his experience, which includes more than 15 years of personal experience with DNA microarray techniques, gene amplification more likely than not correlates with overexpression of mRNA and ultimately with polypeptide overexpression. *See* Tab C, Declaration of Randy Scott, Ph.D. Thus, the '308 patent was issued because the PTO found gene amplification morel likely than not correlated with mRNA and polypeptide overexpression. Applicants respectfully maintain that issuance of the '308 patent is persuasive evidence that the present claims are supported by a specific, substantial, and adequate utility.

US Patent No. 7,276,577 as evidence of utility:

Indeed, the below claim, which is similar to pending claim 27, issued in U.S. Patent No. 7,276,577:

1. An isolated polypeptide comprising:
    a. the amino acid sequence of the polypeptide of SEQ ID NO:14;
    b. the amino acid sequence of the polypeptide of SEQ ID NO: 14, lacking it associated signal peptide; or

c. the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577.

Prior to issuance, this claim was finally rejected and the Assignee of US Patent No. 7,276,577, Genentech, Inc. who is also assignee of the present application, appealed that final rejection. On appeal, the Assignee argued that the above claim was supported by a specific and substantial utility based on microarray data demonstrating amplification of SEQ ID NO:14 in colon, lung and prostate tumors compared to normal tissue. On appeal, the USPTO Board of Patent Appeals and Interferences (hereinafter, the "Board") reversed the Examiner's rejection for lack of utility and found "[t]he use of PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility." *See* Tab D, Decision of the USPTO Board of Patent Appeals and Interferences, Appeal No. 2006-1469 at pages 9-10. Applicants respectfully submit that finding of the Board demonstrates that the claimed polypeptide, PRO347, also has a sufficient utility, particularly as a cancer marker. Indeed, Applicants assert this specific and substantial utility at paragraph 703 of the present application:

> [0703] This example shows that the PRO327-, PRO344-, PRO347- PRO357-, and PRO715-encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. . . . **These amplifications also are useful as diagnostic markers for the presence of a specific type of tumor type.**

Emphasis added.

The Office action alleges that issuance of US Patent No. 7,276,577, and the allowance of the 15 other similar cases discussed in the Amendment and response filed 8/17/07, is not persuasive because those applications presented microarray data of mRNA whereas the present application provides data of amplified genomic DNA. Although the data may be

different, Applicants respectfully maintain that allowance of the 16 patents discussed on page 6 of the 8/17/07 response still is persuasive evidence that the PTO at least acknowledges it is more likely than not that overexpression of mRNA correlates with overexpression of the polypeptide. Indeed, in reversing the Examiner's rejection of the claims (for alleged lack of utility) ultimately issued in US Patent No. 7,276,577, the Board stated, "[a]s demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression." Tab D, Decision of the USPTO Board of Patent Appeals and Interferences, Appeal No. 2006-1469 at page 9. Applicants submitted the Polakis Declarations in this case along with the response mailed September 20, 2005.

Gene amplification data of Example 28 as evidence of utility:

As in the above-discussed patents, Applicants have asserted utility for the instantly claimed PRO347 polypeptide based on amplification of the PRO347 gene in the "gene amplification assay" described in the instant specification in Example 28. Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 28 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 10, including primary lung and colon cancers of the type and stage indicated in Table 9. As a negative control, DNA was isolated from the cells of ten normal, healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 10. As explained at paragraph 0705, the results of TaqMan™ PCR are reported in ΔCt units. One unit corresponds to one PCR cycle of approximately a 2-fold amplification, relative to control, two units corresponds to 4-fold amplification, 3 units correspond to 8-fold amplification, etc. PRO347 showed ΔCt values of approximately 1.01 -2.73 in thirteen lung tumors and 1.1.01-2.1 in nine colon tumors. Thus, Example 28 demonstrates gene amplification of at least 2.00-8.00 fold amplification in 22 lung and colon tumor samples. In support of the showing that the gene amplification values for PRO347 DNA are significant in lung or colon cancer, Applicants submitted, with their Response mailed

June 24, 2003, the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold in a tumor sample relative to a normal sample by the gene amplification assay discussed at pages 119-137 of the present application, is useful as a marker for the diagnosis of cancer:

> [a]n at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number . . . as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Goddard Declaration, paragraph 7 (emphases added).

The Office action alleges that there are several problems with the data provided in Example 28. First, the Office action states that "[h]alf of the colon cancer samples tested positive. Therefore, if a sample were taken from an individual with colon cancer for diagnosis, it is as likely than not that this assay would yield a false negative result." Pages 4-5 of the Office action. Applicants respectfully disagree. For utility, PRO347 does not have to be amplified in every incidence of colon cancer. Indeed, there is no requirement that the claimed PRO347 polypeptide identify all types and cases of colon cancer. Rather, the utility standard only requires that the asserted utility be more likely than not. The data reported at Table 9 reports that PRO347 was amplified in 9 of the 17 colon tumors tested. Thus, amplification of PRO347 more likely than not is useful as a marker for the diagnosis of cancer. Indeed, Applicants note that the claims are not limited colon tissue but rather are directed to colon and lung tissue. The data reported at Table 9 reports that PRO347 was amplified in 13 of the 15 lung tumors tested. Thus, within the scope of the claim it is clear that amplification of PRO347 more likely than not is useful as a marker for the diagnosis of cancer.

Applicants note that the Office action questions the data from the lung tumors based on Hittleman. According to the Office action, Hittleman "teach[es] that damaged, precancerous lung epithelium is often aneuploid." Applicants respectfully disagree that

the teachings of Hittleman are relevant because the amplification of PRO347 was confirmed by framework mapping, which was used to control for aneuploidy. *See, e.g.* paragraphs 0749 and 0731 of the present application. Indeed, Applicants have previously overcome rejections based on alleged failure to correct for aneuploidy. Specifically, as stated in Applicants' response mailed June 24, 2003:

> The data presented in the specification are from experiments using appropriate controls for aneuploidy (see, for example, page 137, lines 13-16). Applicant used framework mapping to control for aneuploidy and to ensure that the observed ΔCt data represent relevant gene amplification. Thus, the reported data are an indication of relevant gene amplification, and support the conclusion that PRO347, and related proteins and antibodies, can be used as a cancer diagnostic.

In response, according to the Office action mailed September 24, 2003, the Examiner "concede[d] . . . that proper controls for aneuploidy were used." Page 6 of the Office action mailed September 24, 2003.

Orntoft, Pollack, Hyman, and the Declaration of Randy Scott, Ph.D. as evidence of utility:

Applicants further note that the Office action states that even if the data is corrected for aneuploidy, the gene amplification data has no bearing on utility of the claimed PRO347 *polypeptide* because allegedly the art demonstrates that a correlation between genomic DNA levels and mRNA levels, or between mRNA and polypeptide levels, cannot be presumed. Page 5 of the Office action. As previously stated, the PTO clearly accepts that overexpression of mRNA more likely than not correlates with overexpression of the polypeptide. *See supra* at pages 5-7.

As the Office action notes, Applicants maintain that Orntoft, Pollack, and Hyman demonstrate that gene amplification levels are more likely than not to correlate with

mRNA levels. Indeed, Applicants maintain that these references support Applicants assertion of utility.

Orntoft *et al.* studies transcript levels of 5600 genes in malignant bladder cancers, many of which were linked the gain or loss of chromosomal material, and found that in general (18/23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Orntoft *et al.* also showed a clear correlation between mRNA and protein expression levels, stating that "[i]n general there was a highly significant correlation ($p<o.oo5$) between mRNA and protein alteration . . . 26 well focused protein whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2, to page 44, column 2). Accordingly, Orntoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

Similarly Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels.

In Pollack *et al.,* the authors profiled DNA copy number alteration across 6,691 mapped human genes in 33 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellant's position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

These references are further supported by the Declaration of Randy Scott, Ph.D. Dr. Scott testified that:

7. The DNA microarray technology is based on hybridizing arrayed nucleic acid probes of known identity with target nucleic acid to determine the identity and/or expression levels (abundance) of target genes. DNA microarrays work by exploiting the ability of a given mRNA molecule to hybridize to the DNA

template from which it originated. By using an array containing many DNA samples, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of genes within a sample by measuring the amount of mRNA bound to each site on the array. The amount of mRNA bound to the spots on the microarray is precisely measured, generating a profile of gene expression in the sample.

8. DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. For instance, if a certain gene is over-expressed in a particular form of cancer relative to normal tissue, researchers use microarray chips to determine whether a drug candidate will reduce over-expression, and thereby cause cancer remission. In addition, if a gene has been identified to be overexpressed in a certain disease, such as a certain type of cancer, it can be used to diagnose that disease. Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetrix, Agilent, Applied Biosystems, and Amersham Bioscience, made microarray technology a core of their business.

Tab C at pages 1-2, paragraphs 7 and 8.

The Office action notes that in addition to the above evidence, Applicants rely on three additional references by Lin *et al.,* Imam *et al.,* and Blancato *et al.* The Office action notes that another reference, Godbout, teaches that amplified genes are overexpressed if they provide a selective advantage and thus, rejects Applicants reliance on these references because the genes studied in each reference allegedly confer a selective advantage for the growth of cancer cells. Applicants respectfully disagree that Godbout limits the teachings of Lin, Imam, and Blancato. However, even if Godbout confines the teachings of these references to the situation where a gene confers a selective advantage, Applicants note that the Godbout does not teach that gene amplification fails to correlate with mRNA expression or polypeptide expression outside of the context of a

gene conferring selective advantage. Indeed, Applicants respectfully submit that Godbout does not apply to PRO347 because amplification of PRO347 was confirmed by epicenter mapping. Specifically, Applicants confirmed that amplification of the closest known epicenter markers did not occur to a greater extent than that of PRO347. Applicants teach that this "strongly suggests that the DNAs tested are responsible for the amplification of the particular region on the respective chromosome." Paragraph 0750. Thus, based on this teaching of the specification, one of ordinary skill in the art would conclude that PRO347 is not a co-amplified gene but rather an amplified gene. In any event, even if Lin, Imam, and Blancato are not applicable in the present situation, Orntoft, Hyman, Pollack, US Patent No. 7,208,308, and the declaration of Randy Scott are persuasive evidence that gene amplification of PRO347 more likely than not correlates with mRNA overexpression.

Pennica, Konopka, and Li do not outweigh the above-discussed evidence:

The Office action relies on references by Pennica, Konopka, and Li as evidence against the above-discussed evidence relied on by Applicants. Applicants respectfully submit that the teachings of Pennica, Konopka, and Li do not outweigh the evidence relied on by Applicants.

As explained above, the patentee of US Patent No. 7,208,308, Genentech, Inc, who is the assignee of the present case, asserted a diagnostic utility for the polypeptide claimed in the '308 patent based on gene amplification resulting in overexpression of the mRNA and subsequently, the protein of the gene. The examiner in that case repeatedly rejected but ultimately accepted that assertion of utility. In rejecting the assertion of utility, the examiner relied on two references relied on in the present case, Pennica and Konopka. Ultimately these references were overcome because the combined teachings of Pennica *et al* and Konopka *et al.* were not directed towards the claimed PRO343, nor towards genes in general but rather are to a single gene or genes within a single family. Thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. For these same reasons, Pennica and Konopka

do not support the present rejection of the claims pending in this application and are overcome.

Indeed, Applicants respectfully disagree that the teachings of Pennica demonstrate that *more likely than not* one of ordinary skill in the art would not expect gene amplification levels to correlate with protein overexpression. First, *WISP-1* gene amplification and RNA expression levels examined in Pennica showed a significant positive correlation. Second, although Pennica stated that *WISP-3* was not significantly amplified, it was amplified (*P*=1.666) and overexpressed. Third, although *WISP-2* gene amplification and RNA expression levels seemed to be inversely related, Pennica suggests that this result might be inaccurate: "[b]ecause the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." *See* Pennica at 14722. Thus, because the RNA expression pattern of *WISP-2* cannot be accurately attributed to gene amplification of *WISP-2,* this result should be disregarded. Indeed, the teachings of Godbout taken with Pennica suggest that Pennica's conclusion that the observed amplification is not actually attributable to *WISP-2* is correct. Moreover, as discussed above, in the present case, appropriate controls for aneuploidy were used and page 137 of the present specification explains the procedures performed to confirm that the observed gene amplification was attributable in the present case to PRO347. Therefore, for this additional reason, Pennica *et al. does not make it more likely than not* that the present invention is not supported by a specific, substantial, and credible utility.

Similarly, Li teaches that "genes that are concurrently amplified because of their location with respect to amplicons" generally do not show correlation between gene amplification and mRNA or polypeptide overexpression. Applicants respectfully disagree that Li is persuasive evidence in the context of the present invention. As discussed above, framework and epicenter mapping analyses were carried out for PRO347 to confirm that PRO347, and not some other gene, is responsible for the observed gene amplification. This coupled with the high rates of observed amplification (approximately 2 to 8 fold amplification in nearly 70% of all tissues tested) indicates that PRO347 gene

amplification more likely than not correlates with overexpression of the PRO347 polypeptide.

Additionally, Applicants note that in Appeal No. 2006-1469, the Board found "there is a strong correlation between mRNA levels and protein expression." In addition, the Board pointed out that the Examiner in Appeal No. 2006-1469 failed to present any evidence specific to the PRO1866 polypeptide that refuted that correlation. Similarly here, Applicants assert a utility based on correlation between gene amplification, increased mRNA expression and polypeptide overexpression. The Examiner in the present case has not identified any evidence specific to PRO347 that demonstrates that gene amplification of PRO347 fails to correlate with overexpression of the PRO347 polypeptide. Thus, for this additional reason, Applicants respectfully submit that this rejection is overcome and respectfully request it be withdrawn.

Section 2107.02 of the MPEP requires the Office to consider whether the *totality of the evidence* submitted regarding the asserted utility demonstrates that the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. For the reasons discussed above, Applicants respectfully maintain that the *totality* of this evidence currently under consideration demonstrates that it is more likely than not that PRO347 is overexpressed in lung or colon tumor tissues. For these reasons, Applicants maintain that this rejection is improper and request that it be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

Claims 27-34 stand rejected under 35 U.S.C. § 112 ¶1, because it is alleged that the presently claimed invention is not supported by a substantial utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, Applicants respectfully submit that the claimed polypeptide is supported by a substantial utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

SUMMARY

Applicants believe that currently pending Claims 27-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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